peptide library with an antibody or antigen-binding derivative thereof that specifically binds to an antigen of interest, thereby identifying a second peptide which binds to said compound and which mimics the binding specificity of said antibody.

REMARKS

The specification has been amended to incorporate the proper claim to priority, as was done in paragraph 4 of the Request for Filing a Continuation Application under 37 C.F.R. § 1.53(b), (attached hereto as Exhibit E).

The specification has been amended to incorporate sequence identifiers pursuant to § 1.821(d). Since a copy of the paper Sequence Listing from application no. 08/488,161 was included when the instant application was filed (see *e.g.*, a copy of the request for filing a continuation application under 37 C.F.R. § 1.53(b), attached hereto as Exhibit E), the above-made amendments do not constitute new matter under 35 U.S.C. § 132.

The specification has also been amended at pages 9, 10, 20, 29, 41, 42, 49, 54, 56 and 65 to capitalize trademarks and insert generic terminology where necessary. The specification was amended at page 46, to update the status of U.S. Patent Application Serial No. 08/127,351. The specification was also amended at page 27 to insert the text of original claims 33 and 36 as filed.

The specification at page 77, line 8 was also amended to correct an obvious typographical error to delete an extra R_9 designated amino acid so only one R_9 amino acid is present.

Prior to the above-made amendments, claims 1 to 12, 14 to 36, 40, and 43 to 45 were pending in the instant application. Claims 1, 5, 7, 9, 11, 12, 14, 18, 20, 22, 25, 28, 29, 31, 32, and 34 have been canceled without prejudice to Applicant's right to pursue the subject matter of the canceled claims in the instant or related patent applications. Claims 2, 6, 8, 10, 15 to 17, 19, 21, 23, 27, 30, 33, 35, and 36 have been amended and claim 46 has been added to more particularly point out and distinctly claim that which Applicant deems to be the subject of the invention. With entry of the above-made amendments, claims 2 to 4, 6, 8, 10, 15 to 17, 19, 21, 23, 24, 27, 30, 33, 35, 36, 40, and 43 to 46 will be pending. Claims 2 to 4, 6, 8, 10, 27, 30, 33, 36, 40, and 43 to 45 are directed to products (*i.e.*, abtides) by process, claims 15 to 17, 19, 21, 23, 24, 35, and 46 are directed to methods for identifying abtides, and claims 23, 24, and 35 are directed to methods of using abtides. A marked up

version of the claims showing the amendments made is attached as Exhibit C and a copy of the claims that will be pending upon entry of the present amendments is attached as Exhibit D.

Claim 2 has been amended to recite a molecule comprising a peptide which mimics the binding specificity of an antibody identified by a two step screening process in which the first and second random peptide libraries are the same or different and which uses the first peptide or a specific binding portion thereof to screen the second random peptide library. Support for these amendments is in the specification at page 24, lines 27-30; page 26, lines 3-10; page 27, lines 33-34 and page 25, lines 26-29.

Claim 6 has been amended to be independent and to recite a molecule comprising a peptide which mimics the binding specificity of an antibody by a method comprising (a) screening a first random peptide library with the antibody or antigen-binding derivative thereof to identify a plurality of different first peptides each of which specifically binds to the antibody or antigen-binding derivative, (b) comparing the sequences of the plurality of first peptides to identify a consensus binding sequence, and (c) screening a second random peptide library with a compound comprising the consensus sequence to identify a second peptide which binds to the compound and which mimics the binding specificity of the antibody. Support for this amendment is in the specification at page 24, line 18 to page 26, line 10.

Claim 8 has been amended to recite that the monoclonal antibody, 7E11-C5 is a murine IgG1 monoclonal antibody which binds specifically to human prostate carcinoma, LNCaP. Support for this amendment is in the specification on page 53, lines 19-20.

Claim 10 has been amended to recite the molecule of claim 2, in which the library is a library of recombinant vectors that express heterofunctional fusion proteins comprising random peptides, said fusion proteins comprising (a) a binding domain encoded by an oligonucleotide of unpredictable nucleotides and (b) an effector domain that enhances expression or detection of the binding domain. Support for this amendment is found in the specification on page 28, lines 15-26.

Claim 15 has been amended to recite a method for identifying a molecule comprising a peptide which mimics the binding specificity of an antibody identified by a two step screening process in which the first and second random peptide libraries are the same or different and which uses the first peptide or a specific binding portion thereof to screen the

second random peptide library. Support for these amendments is in the specification at page 24, lines 27-30; page 26, lines 3-10; page 27, lines 33-34 and page 25, lines 26-29.

Claim 19 has been amended to recite that the monoclonal antibody, 7E11-C5 is a murine IgG1 monoclonal antibody which binds specifically to human prostate carcinoma, LNCaP. Support for this amendment is in the specification on page 53, lines 19-20.

Claim 21 has been amended to recite the method of claim 15, in which the library is a library of recombinant vectors that express heterofunctional fusion proteins comprising random peptides, said fusion proteins comprising (a) a binding domain encoded by an oligonucleotide of unpredictable nucleotides and (b) an effector domain that enhances expression or detection of the binding domain. Support for this amendment is found in the specification on page 28, lines 15-26.

Claims 16, 17, and 23 have been amended to depend from claim 15.

Claims 27 and 30 have been amended to recite compositions comprising the molecules of claims 2 and 8, respectively, by deleting the phrase "therapeutic or diagnostic." Support for these amendments is in the specification at page 43, lines 31-34.

Claim 33 has been amended to recite a molecule comprising a peptide or a binding portion thereof which mimics the binding specificity of a receptor identified by screening a random peptide library with a ligand of interest being a peptide between 5 and 40 amino acids to identify a first peptide that specifically binds to the ligand of interest which represents the portion of a receptor-ligand that is responsible for the specific binding of the receptor to the receptor-ligand. Support for these amendments is in claim 33 as originally filed and in the specification at page 26, line 26 to page 27, line 2.

Claim 35 has been amended to recite to define the internal image is a tumor and to clarify that the molecule is specific to target said tumor. Support for these amendments is in the specification at page 45, lines 26 to 31.

Claim 36 has been amended to recite a method for identifying a molecule comprising a peptide which mimics the binding specificity of an antibody identified by a screening process, which uses the first peptide or a specific binding portion thereof identified from screening a first random peptide library to screen the second random peptide library. Support for these amendments is in the specification at page 24, lines 27-30; page 26, lines 3-10; page 27, lines 33-34 and page 25, lines 26-29.

Claim 46 has been added to recite a method for identifying a molecule

comprising a peptide which mimics the binding specificity of an antibody identified by a screening process which uses the first peptide or a specific binding portion thereof (identified from screening a first random peptide library) to screen the second random peptide library. Support for these amendments is in the specification at page 24, lines 27-30; page 26, lines 3-10; page 27, lines 33-34 and page 25, lines 26-29.

Applicant submits that the above-made amendments are fully supported in the instant application as originally filed, and do not constitute new matter. Applicant respectfully requests that the above-made amendments be entered into the file history of the instant application.

Applicant requests the Examiner to make of record in the present application the references listed on the Revised PTO Form 1449 of the Information Disclosure Statement filed concurrently herewith.

THE OBJECTIONS TO THE DISCLOSURE SHOULD BE WITHDRAWN

The Examiner alleges that Applicant's claim to the priority is confusing and that clarification and/or correction is required. Applicant respectfully points out that paragraph 4 of the Request for Filing a Continuation Application under 37 C.F.R. § 1.53(b), attached hereto as Exhibit E, specifically requests an amendment to the specification incorporating the proper claim for priority. Nevertheless, Applicant has amended the specification to incorporate the proper claim for priority.

The Examiner also points out that the use of trademarks should be capitalized and accompanied by the generic terminology. In response, Applicant has made the requested changes to the trademarks present in the specification, *i.e.*, they have been capitalized and accompanied by generic terminology where necessary.

The Examiner has objected to the disclosure because (1) the status of application Serial No. 08/127,351 at page 46, line 1 has not been updated; (2) the heading "Figure Legends" at page 10 should be changed to --Brief Description of the Drawings--; and (3) the peptide sequences included in the drawings should have a Sequence Identifier Number corresponding to those in the Sequence Listing. In response, Applicant has (1) updated the status of application Serial No. 08/127,351; (2) changed the "Figure Legends" to --Brief Description of the Drawings--; and (3) identified the peptide sequences in the drawings with a Sequence Identifier Number in the Brief Description of the Drawings.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

The Examiner has rejected claims 1 to 45 under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Examiner alleges that the scope of enablement provided in the specification is not commensurate in scope with the claimed molecule of undefined structure obtained via the claimed method having numerous unidentified parameters.

In response, Applicant respectfully points out that claims 13, 37 to 39, and 41 to 42 were canceled, without prejudice, in paragraph 2 of the Request for Filing a Continuation Application under 37 C.F.R. § 1.53(b) (a copy is attached hereto as Exhibit E). Claims 1, 5, 7, 9, 11, 12, 14, 18, 20, 22, 25, 28, 29, 31, 32, and 34 have been canceled, without prejudice. Claims 2, 6, 8, 10, 15 to 17, 19, 21, 23, 27, 30, 33, 35, and 36 have been amended and claim 46 has been added.

The Examiner states that:

> the scope of enablement provided in the specification is not commensurate in scope with the claimed molecule of undefined structure obtained via the claimed method having numerous unidentified parameters such as the first or second library peptide structure, antibody and its binding partner, antigen. The scope entails too numerous variables for not a single defined structure or parameter is recited. However, the specification merely discloses a single, *e.g.*, compound for each of a claimed variable or parameter.

The Examiner states that the present specification discloses only a single abtide that was obtained by screening a random peptide TSAR library with the monoclonal antibody 7E11-C5. The Examiner states that "the specification therefore, lacks not only direction but guidance, as by working example or reasonable assurance, that a molecule obtained by the recited process would be capable of achieving the compound's desired result." The Examiner concludes that "one is left to embark on its own experimentation as to how to proceed in determining which antibody, peptide libraries, or antigen would cooperatively function to achieve the desired molecule having the desired function."

The Examiner then cites three references that allegedly support her position:

Lenstra et al., 1992, "Isolation of sequences from a random-sequence expression library that mimic viral epitopes", J. Immunol. Methods 152:149-157 (Lenstra) (Reference BB of the Information Disclosure Statement filed concurrently herewith); Gallop et al., 1994, "Applications of combinatorial technologies to drug discoveries. 1. Background and peptide combinatorial libraries", J. Med. Chem. 37(9):1233-1251 (Gallop) (Reference AT of the Information Disclosure Statement filed concurrently herewith); and Lam et al., 1991, "A new type of synthetic peptide library for identifying ligand-binding activity", Nature 354:82-84 (Lam) (Reference BJ of the Information Disclosure Statement filed concurrently herewith).

Further, the Examiner states that:

> The particular embodiments of the invention requires that epitope to which an antibody specifically binds is shown, page 26, lines 13-15. Accordingly, if either the ligand or the peptide libraries is undefined how could specific binding and isolation of the peptide be achieved?

The Examiner also states that "there is no way of reliably forecasting the structure of the peptide that would mimic the ligand in function or activity given the numerous variables such as the ligand, peptide libraries, substance of interest, etc. as broadly claimed."

Lastly, the Examiner alleges that the specification further fails to teach how to use the claimed molecule as a therapeutic composition because there is no disclosure in the specification as to the therapeutic effect of any of the recited molecules.

THE LEGAL STANDARD

As a preliminary matter before addressing the Examiner's arguments, Applicant briefly reviews certain relevant legal principles. To comply with U.S.C. § 112, first paragraph, a specification need only teach those of skill in the most relevant arts to practice the claimed invention (Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984)).

Further, a specification and claims of corresponding scope must be taken as *prima facie* in compliance with § 112 unless specific and articulated reasons to the contrary are offered.

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and

> defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.Fiers v. Revel, 984 F.2d 1164, 1171-72 (Fed. Cir. 1993) (citing In re Marzocchi, 439 F.2d 220, 223, (C.C.P.A. 1971)) (emphasis added). The examiner bears the initial burden of asserting reasons for such doubt credible to one of skill in the art. Id.

A *PRIMA FACIE* CASE FOR THIS REJECTION HAS NOT BEEN MADE

In response, Applicant respectfully submits that the Examiner has not met the necessary burden that the Patent and Trademark Office bears in establishing a *prima facia* case of non-enablement (In re Oetiker, 24 U.S.P.Q. 2d 1443, 1445 (Fed. Cir. 1992). The Examiners' contention and argument in support of the instant rejection are entirely conclusory. No objective and relevant evidence has been adduced that would cast doubt on the ability of one of skilled in those arts most closely associated with Applicant's claimed invention to practice their invention without undue experimentation. The relevant standard for rejection has simply not been met.

Applicant respectfully disagrees with this rejection. First, Applicant points out that independent amended claims 2, 6, 33, and 36 (and claims 8, 27, 30, 33, and 45 dependent thereon) are product-by-process claims. As stated in the M.P.E.P. § 2173.05(p),

> "[a] product-by-process claim, which is a product claim that defines the claimed product in terms of the process by which it is made, is proper." (citations omitted) A product-by-process claim is enabled if upon a showing that one of ordinary skill in the art possesses the expertise to produce the claimed product according to the recited process without undue experimentation. *Ex parte Kung*, 17 U.S.P.Q.2d 1545, 1546 (BPAI 1990).

As explained below, the process for obtaining molecules that comprise peptides that mimic the binding specificity of an antibody are enabled by the specification.

Second, Applicant respectfully disagrees with the Examiner's position that the scope of the claims is not commensurate with the specification. The Examiner appears to be positing a rule that an Applicant must be limited to claiming only what is present in the working examples. This is not the law. In fact, there is no requirement that an application have any working examples, even when the invention involves a complex technology. See

In re Strahilevitz, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982).

> The examiner reasoned that because of the breadth of the invention, a large number of examples (50 to 100) would be required to enable one of ordinary skill in the art to make and use the invention. ... We recognize that working examples are desirable in complex technologies and that detailed examples can satisfy the statutory enablement requirement. Indeed, the inclusion of such examples here might well have avoided a lengthy and, no doubt, expensive appeal. Nevertheless, as acknowledged by the board, examples are not required to satisfy section 112, first paragraph. ... Therefore, the examiner's statement that the "nearly universal applicability" alleged for the invention necessitated numerous examples was erroneous. Although the invention is applicable to a large variety of haptens and antigens, the examiner offered no reason why these different compounds would require different techniques or process parameters. [citations omitted, emphasis added]
>
> 668 F.2d at 1232, 212 U.S.P.Q at 563.

Strahilevitz is consistent with other case law in which courts have taught that it is not necessary to provide examples that encompass the entire realm of any and all species in a claimed genus. See *In re Bowen*, 492 F.2d 859, 181 U.S.P.Q. 48 (C.C.P.A. 1974):

> Accordingly, there appears to be no basis for the non-enablement rejection on the theory that claims read on undisclosed polymers. While the claims literally comprehend numerous polymers in addition to the one specifically described in appellant's specification, nylon 66, no persuasive reason has been given by the Patent Office why the specification does not realistically enable one skilled in the art to practice the invention as broadly as it is claimed.
>
> 492 F.2d at 863, 181 U.S.P.Q. at 51-52.

As explained below, the Examiner has given no persuasive reason why one of ordinary skill in the art would be unable to practice the invention as presently claimed. All the Examiner has done is to point out that the Applicant did not provide examples for every species that might be encompassed by the present claims. But as *Bowen* demonstrates, more is necessary for a conclusion of non-enablement.

The Examiner has stated that the Applicant does not teach all ligands that may be used in the present claims. As discussed above, this is not necessary. Applicant respectfully points out to the Examiner that the claims have been amended to recite a

molecule comprising a peptide that mimics the binding specificity of an antibody (*e.g.*, claim 2) and uses the antibody to screen the first random peptide library. Moreover, the Applicant wishes to point out that the antibody to be chosen is only used in the first step of the claimed invention (*e.g.*, step (a) of claim 2)[1]. The step of screening a library with a chosen antibody was well known in the prior art; indeed, the specification explicitly discloses a wide variety of antibodies that have been used in the first step. See Section 2.2, at pages 6-8.

Since what is well known in the prior art need not be explicitly taught[2], the Applicant was under no obligation to provide detailed teachings as to how to practice this first step, including which antibodies may be used. Nevertheless, the Applicant has provided detailed teachings regarding how to carry out this step with numerous antibodies and libraries (see Section 2.2, at pages 6-8, and Section 5, at pages 23-24, where various ligands are disclosed; Section 5, at pages 14-22, where various libraries are disclosed; and Section 5, at pages 23-35 (especially pages 28-29), where screening methods are disclosed). Moreover, as in *Strahilevitz*, the Examiner has offered no reason why the use of any non-exemplified antibodies would require different techniques from those required for the use of the antibody in the working example.

The Applicant was the first to conceive that the product of the first step can be used to screen the same, or a different, library as was used in the first step in order to obtain "abtides," *i.e.*, peptides that were functional mimics of the antibody, with a reasonable expectation of success. With respect to this second step, (*e.g.*, step (b) of claim 2), the Applicant has provided abundant teachings of the libraries that may be used in this second step. See the specification at pages 14-22 for a detailed description of such libraries. Thus, contrary to the Examiner's contention, the Applicant has provided numerous examples of the different antibodies, first random peptide library, and second random peptide library. Moreover, the same routine screening steps may be used in step (b) as in step (a).

In addition, the Applicant has provided a working example, in which the TSAR-9 library was successfully screened to isolate abtides. The Examiner has provided no persuasive reasons why the teachings of the specification at pages 14-22 and the working example are not broadly applicable and would not, combined with the teachings of the prior

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[1]Claims 33 and 36 omit specifying the first step and start with step 2.

[2] *See In re Wands*, 858 F.2d 731, 735, 8 U.S.P.Q.2d 1400, 1402 (Fed. Cir. 1988): "A patent need not disclose what is well known in the art."

art, enable the practice of the claimed invention. The burden is on the Examiner to provide evidence or reasoning (not just speculation) as to why the invention is not enabled. See *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971), where the United States Court of Customs and Patent Appeals stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein .... [emphasis in original]
>
> 439 F.2d at 223, 169 U.S.P.Q. at 369.

With regard to the references Lenstra, Gallop, and Lam, these references all disclose subject matter that corresponds only to the first step of the process for identifying molecules of the present invention. These references are all primarily directed to the successful practice of that first step. The Applicant fails to see how the successful screening step taught by these references can support a conclusion that the molecules of the present invention are not enabled. Rather, these references indicate the state of the art which had as part of its content the fact that a step of screening random peptide libraries was routine. Thus, these references support, rather than argue against, the conclusion that the process for identifying the claimed molecules of the presently claimed invention is enabled.

With regard to Lenstra, the Examiner stated:

> the number of antigenic clones in the library depended on the antibody used for immunoscreening.

Presumably, the Examiner is here referring to the results reported in Table II of Lenstra on page 152. These results show that, *e.g.*, screening with antibody 6A.A6 gave 7 positive clones, screening with antibody 57.9 gave 1 positive clone, and screening with antibody 1G.A7 gave no positive clones. It is the Applicant's view that the fact that the number of positives might differ from antibody to antibody is not germane to the patentability of the present claims. Rather, what is relevant about the results of Lenstra is that there was a reasonable rate of success for the overall process of screening the library. Table II shows that of the 9 antibodies tested, 4 (44%) gave positive results. Where screening experiments such as those described in the present application or in Lenstra are concerned,

the Court of Appeals for the Federal Circuit has held that invarying success is not necessary for enablement. A reasonable number of failures would be tolerated and expected by one of skill in the art as long as the prospect for obtaining some reasonable level of positive results exists. Moreover, the Court has stated that 44% is a respectable level of success. See *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988):

> Enablement is not precluded by the necessity for some experimentation such as routine screening.
>
> 858 F.2d at 736-737, 8 U.S.P.Q.2d at 1404.
>
> Wands views the data quite differently. Only nine hybridomas were actually analyzed beyond the initial screening for HBsAg binding. Of these, four produced antibodies that fell within the claims, a respectable 44 percent rate of success. [emphasis added]
>
> 858 F.2d at 739, 8 U.S.P.Q.2d at 1406.

It is clear that Lenstra viewed the results of Table II as a success. See page 155, left column, second paragraph:

> We wished to answer two questions: (1) Can we identify mimotopes by immunoscreening of a bacterial random-sequence expression library with antiviral mAbs? ... We have indeed demonstrated that sequences which mimic a viral epitope can be identified by immunoscreening of a hexa- or octapeptide library.

See also page 155, right column, fourth paragraph: "We conclude that screening of random-sequence expression libraries is a general and efficient approach to the mapping of B cell epitopes." [citations omitted]

The Examiner also stated, with respect to Lenstra:

> And, mimotopes are constructed and selected by satisfying the binding requirement of one particular antibody. Consequently, a mimotope may be a reconstruction of the antigenic surface that is biased [sic] on only one antibody rather than a realistic representation.

Here, the Examiner is presumably referring to the discussion on page 156, left column, third paragraph:

> From the outset it was suggested that mimotopes may also be used to formulate peptide immunogens for vaccine development. Scientifically challenging as this may be there

> are a few caveats. Firstly, one should discriminate between structural and antigenic equivalence. Mimotopes are constructed or selected by satisfying the binding requirements of one particular antibody. Consequently, a mimotope may be a reconstruction of the antigenic surface that is biased by only one antibody rather than a realistic representation. In fact, we have observed that the mimotopes of sites II and IV from TGEV are not recognized by mAbs specific for other epitopes within the same site. [citations omitted]

This paragraph refers to the possibility of using mimotopes as immunogens that mimic the antigen recognized by the antibody. In order to be useful for the purpose contemplated by Lenstra, *i.e.*, as vaccines, such mimotopes should be a "realistic representation" of a particular antigenic site. That is, the mimotopes of Lenstra should be capable of binding to, and therefore stimulating the production of (when used as vaccines), a variety of antibodies directed to the antigenic site.

In the process for identifying molecules of the present invention, the "first peptide" of the present claims can be thought of as the correlate of the mimotopes of Lenstra. In contrast to the requirement of the mimotopes of Lenstra that the mimotopes be capable of binding to more than just the particular antibody that is used to identify them, the first peptides of the present invention have no such requirement. Even if the first peptides bind only to the particular ligand that is used in the first step of the invention to identify them, the first peptides can still be used for the second screening step. There is no requirement that the first peptide bind to any natural ligands other than the antibody that is used to identify it in the first screening step. This is because the presently claimed molecules (abtides) mimic the binding specificity of the <u>particular</u> antibody that is used in the process to identify the molecules. See, *e.g.*, amended claim 2.

The Examiner has provided no reason why the first peptide must be a "realistic representation" of the antibody in order for the first peptide to be used in the second screening step. The Applicant has provided a working example which demonstrates that this is not necessary.

If the Examiner is alluding here to the possibility that the presently claimed molecules may not be useful as immunogens, while the Applicant respectfully disagrees, the Applicant wishes to point out that the present claims are not directed to the use of the claimed

molecules as immunogens.[3] The claims as presently amended are directed to molecules that mimic the binding specificity of an antibody and a composition thereof. The Applicant need show utility for only one disclosed purpose. *See Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958, 220 U.S.P.Q. 592 (Fed. Cir. 1983, *cert. denied*, 469 U.S. 835 (1984); *Ex parte Lanham*, 121 U.S.P.Q. 223 (Pat. Off. Bd. App. 1958). Thus, the potential problems discussed by Lenstra on page 156, left column, third paragraph, with respect to the use of Lenstra's mimotopes as immunogens for the preparation of vaccines are irrelevant to the question of whether the invention defined by the present claims possesses utility. Furthermore, even if the statement by Lenstra that mimotopes raised by screening with one antibody may not bind a second antibody were extrapolated to abtides, it would still be irrelevant to the patentability of the present claims. The present claims contain no limitation that the abtides produced by the claimed methods must mimic anything other than the binding specificity of the antibody used to identify them. Thus, there is no requirement that the Applicant show that an abtide identified by the recited process utilizing an antibody must mimic the binding specificity to any other antibody.

With regard to Gallop, the Examiner stated: "Note further Gallop's (Ref. AT) disclosure as to the criteria and constraints that must be imposed on the creation of libraries that is used for drug discovery."

Gallop is a review of the uses of various types of random peptide libraries for drug discovery. Such libraries may be used in the steps of the present invention. Gallop demonstrates the routine nature of methods of screening such libraries and thus supports the position that the present claims are enabled. Moreover, Gallop discusses approaches for satisfying the "criteria and constraints" alleged by the Examiner, and thus shows that the art

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[3] With respect to utility, the specification teaches that abtides may be used in a wide variety of ways that have nothing to do with the process of making immunogens. For example, the specification teaches that abtides may be used in immunoassays such as, for example, western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assays), "sandwich" immunoassays, dot immunoblot assays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, immunoaffinity chromatography, and flow dipstick assays (See page 40, lines 3-18). The specification also teaches the use of abtides for *in vivo* localization to prostate carcinoma in a xenograft model (See page 10, lines 5-8). The specification also teaches the use of abtides for imaging at page 45, line 22 to page 48, line 21. This use for imaging is exemplified in the working examples at Section 6.1.4, pages 65-71.

taught how to use libraries in such manner. Furthermore, the Applicant notes that the abtides identified by the recited two step process have uses other than only as drugs (see footnote 2, above). Gallop is cited in the specification at page 16, lines 4-5.

With regard to Lam, the Examiner stated: "Also, see Lam et al. (Nature)." Lam is a disclosure of the use of a particular type of peptide library, the so-called "peptides on beads" type. Lam is a report of the successful use of such library, and thus, if it has any relevance at all to the question of the enablement of the present claims, supports the position that those claims are enabled. The specification states that this library may be used in the process for obtaining abtides of the present invention (see page 16, lines 1-2).

Applicant also disagrees with the Examiner's contention that the determination of the scope and content of the claims places an undue burden on persons skilled in the art, *i.e.,* undue experimentation (Office Action, page 7.) On the contrary, it would not require undue experimentation to practice the recited two step or one step process to identify molecules of the presently claimed invention.

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. Fields v. Conover, 170 U.S.P.Q. 276, 279 (CCPA 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. Id.

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in In re Angstadt, 190 U.S.P.Q. 214 (CCPA 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue"

since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original).

The present application provides ample guidance on how to identify molecules of the invention as presently claimed by performing a two step or one step process.

First, a random peptide library is screened with an antibody to obtain a first peptide. Second, the first peptide is then used as the ligand to screen a random peptide library to obtain a second peptide. Alternatively, the first step can be bypassed if an epitope is available to perform only the second step (*e.g.*, claims 33 and 36).

The result of the methods is the molecule comprising a peptide (the second peptide) which mimics the binding of the antibody used initially in the first screening step.

The quantity of experimentation involved is minor, particularly given the teachings in the specification and the state and level of skill in the art at the time of the invention and filing of the application. Screening of peptide libraries was frequently carried out by laboratory technicians in a few weeks time.

The nature of the invention is identifying molecules by the process which combines a first screening step using an antibody as a ligand with a second screening step using the peptide identified in the first step. Alternatively, the second step alone can be performed using an epitope that is a peptide. The individual screening steps are still routine but it is the utilization of the random peptide identified in the first screening step as a ligand for the second screening step that is the crux of the invention. The specification and knowledge in the art teaches how to obtain the first peptide used as a ligand in the second step.

An enabling description for a process or method requires sufficient disclosure as to "how to carry out the claimed process." *In re Barrett*, 440 F.2d 1391, 1392 (C.C.P.A. 1971). For example, in *Barrett*, the court held that a claimed process for producing thoria sol by electrodialysis using "an anion permeable membrane" was sufficiently enabled without restriction as to the type of anion permeable membrane to be used. 440 F.2d at 1393. The court found that although "the proper selection of the membrane *is* critical because certain anion permeable membranes might not be operative in the process, there is nothing in the record to suggest that, even if this is so, the selection of an appropriate membrane would not

have been within the ordinary skill in this art at the time appellants' parent application was filed." 440 F.2d at 1392. "If selection of an appropriate membrane would have been within the ordinary skill in the art at that time, appellants; disclosure is just as sufficient as if the selection criteria were set forth at length in the specification." 440 F.2d at 1393 (citation omitted) (emphasis added).

In the present case, Applicant has provided sufficient guidance and direction in which the experimentation should proceed to enable one of ordinary skill in the art to identify molecules which mimic the binding specificity of an antibody by practicing the recited two step or one step process. The selection of ligands (*i.e.*, antibodies), libraries and screening methods that can be used in the two step process to identify the claimed molecules was within the skill of one in the art at the time this invention was made and this application was filed.

The selection and use of ligands *e.g.*, antibodies, to screen libraries of random peptides were known to one of ordinary skill in the art as explained in the illustrative examples in the specification, section 2.2, pages 6-8.

The Examiner has quoted the specification by stating that "screening of peptide libraries has generally been confined to the use of a restricted number of ligands." Applicant respectfully points out that the Examiner has used this statement out of context allegedly to exemplify that the state of the art for screening with ligands was "undefined," and that the specification lacked sufficient guidance in this step. However, the quote should be read in context with the other statements that "Most commonly the ligand has been an antibody" and "Thus given an available antibody, peptide libraries are excellent sources for identifying epitopes or epitope like molecules of that antibody." Therefore, screening with an antibody to provide a first peptide was well known in the art. See the specification, Section 2.2, pages 6-8, Section 5, page 12, lines 17 to page 13, line 2, and page 23, line 26 to page 27, line 2. There are many antibodies available, see *e.g.*, the ATCC catalog and many commercial sources, any of which can be used to practice the invention. Also see the specification at Section 5.3.1, pages 35-37 to Section 5.4, pages 37-39.

As set forth in the specification, chemically synthesized and biological random peptide libraries were also known in the art (see the specification, Sections 2.1, 5.1, 5.1.1, and 5.1.2, pages 1-6 and 14-22 for illustrative examples).

Methods for screening such libraries using ligands such as antibodies using a

single screening step were already well known to one of ordinary skill in the art at the time of the invention. See the specification, Section 5.1.1 at page 15 and Section 5.3 at pages 24-26 describing illustrative examples of known methods of screening.

As explained above, the specification sets forth the variables to be selected to accomplish such screening steps and criteria for their selection was already known in the art. It would merely be routine for one of ordinary skill in the art to select an antibody of choice to screen a chemically synthesized or biological library of random peptides already known and available in the art using known single step screening methods. Most importantly, the Applicant provided a working example for the claimed method of identifying a peptide which mimics the binding specificity of an antibody.

The Examiner stated in the Office Action that "particular embodiments of the invention requires [sic] that epitope to which an antibody specifically binds is known, page 26, lines 13-15." Applicant respectfully points out to the Examiner that the cited page 26, lines 13-15 of the specification explains that one embodiment of the invention utilizes known epitopes to which an antibody specifically binds (as recited in amended claims 33 and 36). Further, if the sequence of the epitope is known, the first screening step is not necessary to identify molecules that mimic the binding specificity of an antibody. For other embodiments of the invention, as previously discussed above, it is not necessary to know the sequence of an epitope. One merely needs to perform the first screening step with an antibody of choice, and then the second screening step using the first peptides to identify the molecules that mimic the antibody used in the first screening step. Therefore, the present invention has a particular embodiment for when the amino acid sequence is known for an epitope, and knowledge of the amino acid sequence of an epitope is not necessary for all embodiments of the invention.

Contrary to the Examiner's statement, the presently claimed methods do not require one of ordinary skill in the art to "reliably [forecast] the structure of the peptide that would mimic the ligand..." (Office Action, p. 8). The present invention does not require any prior knowledge of structures or amino acid sequences of peptides to identify those that mimic a preselected ligand (*i.e.*, an antibody). Quite the opposite, the presently claimed invention identifies molecules utilizing libraries containing random peptide sequences and requires no prediction of peptide structures. See the specification at pages 14-22. The use of random peptide libraries removes any burden on one of skill in the art to design any peptides,

and the synthesis of random peptide libraries was known in the art. Examples of both chemically synthesized or biological libraries are noted in the specification at pages 14-22. Therefore, the generation of peptides in random peptide libraries for screening does not impose an undue burden upon persons skilled in the art.

Further, the Examiner states that "the ligand is but one of the numerous undefined parameters that is instantly claimed" (Office Action, p. 5). As stated above, it would merely be routine for one skilled in the art to select an antibody of interest to use to screen random peptide libraries using the claimed invention's two step method to identify the presently claimed molecules.

A ligand in the art of screening combinatorial libraries is the molecule used as the target in screening a library, the subject of the screen, the molecule for which one wishes to identify a binder from the library. In the specification, an abtide of the invention identified by the two step process binds to a ligand. The two step process of the invention uses a first target ligand and a second target ligand. According to the presently claimed invention, first target ligand is an antibody and is the subject of the first screening step, page 13, lines 13-15. The second target ligand is a specific binding partner of the antibody (first peptide) and is the subject of the second screening step, page 13, lines 30-35.

Random peptide libraries are known in the art as having a plurality of vacant positions each occupied by any one of various amino acids. "Random" refers to the fact that at any given position it can not be predicted which of the 20 naturally occurring amino acids will appear. See specification at page 15, lines 13-23. Further, the random peptide libraries can be chemically synthesized libraries, examples of which are described by Fodor et al., 1991, Science 251:767-773; Houghten et al., 1991, Nature 354:84-86; Lam et al., 1991, Nature 354:82-84; (references BL, BK and BJ, respectively in the Information Disclosure Statement filed concurrently herewith); Scott and Smith, 1990, Science 249:386-390; Cwirla et al., 1990, Proc. Natl. Acad. Sci. USA 87:6378-6382; Dower & Cwirla, PCT Publication WO 91/19818 dated December 26, 1991; Devlin et al., 1990, Science 249:404-406; Christian et al., 1992, J. Mol. Biol. 227:711-718; Lenstra, 1992, J. Immunol. Meth. 152:149-157; and Cull et al., 1992, Proc. Natl. Acad. Sci. USA 89:1865-1869 (references BQ, BS, AM, BU, BB, and BC, respectively, in the Information Disclosure Statement filed concurrently herewith).

As set forth in the specification, a first random peptide library is simply a

random peptide library used in the first screening step, and a second random peptide library is that used in the second screening step of the invention. The specification teaches that this library may be the same or different from the first random peptide library.

Applicant respectfully points out to the Examiner that independent claims 2, 6, 8, 10, 15, 27, 30, 33, and 36 have been amended has been added to more distinctly recite and claim specific embodiments of the present invention. Claims 2, 6, 33 and 36 (and claims dependent thereon) have been amended to recite molecules comprising peptides which mimic the binding specificity of an antibody.

It would not constitute undue experimentation for one skilled in the art to select ligands (*i.e.*, antibodies), libraries and screening methods to produce molecules comprising peptides which mimic the binding specificity of an antibody by practicing the two step or one step process because the selection of a ligand, a random peptide library and methods of screening such libraries are routine in the art and the specification provides guidance as to the selection of these variables.

The Examiner has quoted a portion of the specification relevant to the elution conditions during screening and that various conditions may need to be tested in order to determine optimal elution conditions as an example that the Applicant recognizes the high unpredictability in the art. Applicant respectfully points out that the Examiner has cited the specification out of context (Office Action pp. 6 to 7). Contrary to the Examiner's assertion, the testing of various conditions to determine optimal elution conditions is well known to one of skill in the art. As cited in In re Wands, the test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). It would not constitute undue experimentation for one of skill in the art to determine optimal elution conditions during library screening, as such techniques are routine.

Applicant also disagrees with the Examiner's contention that the specification fails to teach how to use the claimed molecules as a therapeutic composition as recited in claims 26-28 and 30-31 allegedly because the disclosure does not disclose a therapeutic effect of any of the recited molecules.

However, in order to advance prosecution of particular embodiments of the present invention, Applicant has canceled claims 26, 28, and 31 and amended claims 27 and 30 by deleting the words "therapeutic or diagnostic", to recite compositions comprising the

molecules of claims 2 and 8, respectively, and a carrier. These amendments obviate this ground for rejection.

Accordingly, Applicant submits that the above amendments and remarks overcome or obviate this rejection and its withdrawal is requested.

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1 to 45 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding the language of the claims, Applicant points out that what is required by the second paragraph of § 112 is that the claims set out and circumscribe the particular area which the patent applicant regards as his invention with a reasonable degree of precision and particularity. In re Moore, 439 F.2d 1232 (C.C.P.A. 1971). "[A]cceptability depends on 'whether one of ordinary skill in the art would understand what is claimed ... in light of the specification,' even if experimentation may be needed." Andrew Corp. v. Gabriel Electronics, Inc., 847 F.2d 819, 821 (Fed. Cir. 1988) (citing Seattle Box Co. v. Industrial Crating & Packing, 731 F.2d 818, 826 (Fed. Cir. 1984)), cert. denied, 488 U.S. 927 (1988).

(A) The Examiner alleges that "claims 1 and 2, for example, use several terms that appear to mean the same thing thus, producing confusion and ambiguity." First, the Examiner states that, "the first and second ligand which is a specific binding partner of the substance of interest appears to be the peptide as recited in the preamble." Second, the Examiner considers it unclear "whether the compound which comprises the peptide obtained from the first random library includes other components besides the first peptide and how or whether the second peptide indeed binds to the substance of interest."

Applicant respectfully disagrees with this ground for rejection. Applicant directs the Examiner's attention to the specification at page 9, lines 6-8 which states that "abtides specifically bind to a ligand of interest, in which the ligand is a specific binding partner of the larger molecule (*e.g.*, antibody or receptor)."

However, in order to more particularly point out and distinctly claim the invention, 2 has been amended to delete the phrase "antigen of interest" and to recite "a method of identifying a peptide which mimics the binding specificity of an antibody." Claim 1 has been canceled, without prejudice.

Further, Applicant respectfully points out to the Examiner that the ligand of *e.g.*, claim 2 (antibody) is used to screen the first random peptide library to isolate a first peptide, also known as an epitope mimic (or mimetope, in the case of using an antibody ligand, like in claim 2). See the specification at page 24, line 18 to page 25, line 36.

The molecule comprising the first peptide is then used to screen a second peptide library. See specification at page 26, lines 1-10.

The specification describes how to construct compounds or molecules comprising the first peptide when it explains:

> Once the amino acid sequence of the epitope or mimetope is known (or a portion thereof, which mediates binding), a molecule, preferably a peptide, is produced comprising that amino acid sequence which mediates binding. This peptide may be synthesized chemically, or, alternatively, may be produced by methods involving recombinant DNA. This peptide may contain only the amino acids of the epitope or mimetope or, preferably, it may contain additional amino acids or non-amino acid moieties to aid in identifying or recovering the epitope or mimetope peptide and any new peptide binders found in the subsequent screening step discussed below.See specification at page 25, lines 26-36.

The second screening step can also be accomplished using a "molecule comprising the first peptide," for example, phage expressing said first peptide; fusion proteins containing said first peptide (e.g. with pIII protein of phage, see specification page 17, lines 10-14, GST, etc. as known in the art); chemically synthesized compounds having the first peptide sequence which may also include additional amino acid or non-amino acid sequences. See specification page 25, lines 31-36. The abtides may also be linked to a variety of non-peptide moieties such as toxins, drugs, polysaccharides, nucleotides, oligonucleotides, labels, biotin, fluorescent tags, imaging reagents, hydrocarbon and linkers. See specification page 23, lines 14-26. See also specification at page 23, line 27 to page 24, line 2, and page 29, lines 7-12. The specification also teaches by way of example that biotinylated first peptides (another example of a "molecule comprising the first peptide") also can be used to screen the second peptide library. See specification page 52, line 35 to page 59, line 10.

Applicant points out that the claims have also been amended to more specifically point out that the second peptide mimics the binding specificity of said receptor or antibody, respectively. The second peptide is identified from the second random peptide library, and therefore is clearly not the initial receptor or antibody.

Applicant submits that the above amendments and remarks overcome this rejection and its withdrawal is requested.

(B) The Examiner alleges that the claimed "substance of interest" of claim 1 or the "antigen of interest" of claim 2 appear to connote a multitude of substances or antigens.

The Examiner here gives no reason for this rejection for alleged indefiniteness other than that the rejected claims are broad. The Applicant wishes to point out that mere breadth does not make claims indefinite. *See Application of Gardner*, 427 F.2d 786, 788, 166 U.S.P.Q. 138, 140 (C.C.P.A. 1970):

> We do not find any indefiniteness in any of the claims by reason of their failure to name a host. They are merely broad in this respect and cover the composition and the method when administered or applied to any host capable of enjoying the benefits of an antidepressant drug. Breadth is not indefiniteness. [emphasis added]

Nevertheless, in order to more particularly point out and distinctly claim embodiments of the present invention, Applicant has amended claim 2 to delete "substance of interest" and "antigen of interest", respectively. Claim 1 has been canceled, without prejudice.

Applicant submits that the above amendments and remarks overcome this rejection and its withdrawal is requested.

(C) The Examiner alleges it is unclear, "within the claimed context, in what aspects the first and second random peptide libraries are different from each other."

The Applicant submits that the specification, at page 27, lines 3-4, makes it clear that the first and second random peptide libraries may be the same or they may be different: "The peptide libraries that are used in the first and second screening steps may be the same or different." What is deemed to make one peptide library different from another peptide library would be well known to one skilled in the art, *e.g.*, differences in the forms of library members, differences in complexity, differences (for biological expression libraries) in the type of recombinant host, mode of expression, *etc.*

However, in order to more particularly point out and distinctly claim the present invention, claims 2, and 6 have been amended to recite that the second random peptide library is the same or different from said first random peptide library. Claims 1 and 5 have been canceled, without prejudice.

Applicant submits that the above amendments and remarks overcome this rejection and its withdrawal is requested.

(D) The Examiner alleges that the recited antibody, 7E11-C5, is improper, and the Examiner requires the Applicant to provide either the structure or the function of the antibody.

In response, claims 8 and 19 have been amended to recite that monoclonal antibody 7E11-C5 is a murine IgG1 monoclonal antibody which binds specifically to human prostate carcinoma cell line LNCaP, as produced by the hybridoma deposited with the ATCC and assigned accession number HB 10494. This deposited hybridoma became available to the public upon issuance of U.S. Patent No. 5,162,504 issued November 10, 1992.

Applicant submits this amendment overcomes this rejection and its withdrawal is requested.

(E) The Examiner alleges that claim 13 does not substantially differ from claim 12. The Examiner stated: "While claim 23 [12] recites for a molecule comprising the recited sequences, it appears that the peptide sequence of ID. No. 2 consists of only the amino acid residues as recited in claim 13."

Applicant respectfully points out that claims 13, 37 to 39, and 41 to 42 were canceled, without prejudice, in paragraph 2 of the Request for Filing a Continuation Application under 37 C.F.R. § 1.53(b) (a copy is attached hereto as Exhibit E). Claim 12 has been canceled, without prejudice.

Applicant submits that the this rejection has been obviated and its withdrawal is requested.

(F) The Examiner alleges that the metes and bounds of the claimed "binding portion" of claim 12, for example; "plurality of molecules", of claim 32; "peptide of length between 5 and 40 amino acids", of claim 33, for example, are indefinite. The Examiner also states that "it is not clear as to the minimum and maximum numbers of molecules that could be obtained from the screening of the libraries."

Applicant respectfully disagrees with these grounds for rejection. Applicant notes that claims 12 and 32 have been canceled, without prejudice.

The phrase "peptide of length between 5 and 40 amino acids", as used in claim 33 is taught in the specification at page 14, line 3-5 which states that "[t]he present invention provides a method to successfully screen against very small peptide or protein targets *e.g.*, 5

to 40 amino acids. . . ." Clearly, the recited peptide contains a total number of amino acids that is in the range of 5 to 40 amino acids. Therefore, the phrase is not indefinite. Further, the Examiner has failed to assert a reason why one of ordinary skill in the art would not understand the meaning of this phrase.

Lastly, Applicant points out that the number of molecules that could be obtained from screening a library depends upon the ligand (*i.e.*, antibody), the characteristics of the library and the extent of screening performed. The Examiner has set forth no reason why one of ordinary skill in the art would not understand this fact. Therefore, the claim is not indefinite as to the number of molecules one would obtain.

Applicant submits that the above amendments and remarks overcome this rejection and its withdrawal is requested.

(G) The Examiner alleges that the recitation of claim 20 of a "library of recombinant vectors that express a plurality of heterofunctional fusion proteins lack antecedent basis of support from the base claim 14 which recites a library of peptides" and that "the recitation of [an] 'unpredictable' nucleotides goes against the requirement of the law that the claims be definite.

In response, Applicant respectfully point out that claim 20 has been canceled, without prejudice. Applicant submits that the this rejection has been obviated and its withdrawal is requested.

(H) The Examiner alleges that claim 25 is "confusing since the method encompasses two method steps *i.e., in vivo and in vitro*."

In response, Applicant respectfully point out that claim 25 has been canceled, without prejudice. Applicant submits that the this rejection has been obviated and its withdrawal is requested.

(I) The Examiner alleges that claim 33 is "indefinite as to how the method can produce[d] different peptide lengths."

The phrase "peptide of length between 5 and 40 amino acids", as used in claim 33 is taught in the specification at page 14, line 3-5 which states that "[t]he present invention provides a method to successfully screen against very small peptide or protein targets *e.g.*, 5 to 40 amino acids. . . ." Clearly, the recited peptide contains a total number of amino acids that is in the range of 5 to 40 amino acids. Therefore, the phrase is not indefinite. Further, the Examiner has failed to assert a reason why one of ordinary skill in the art would not

understand the meaning of this phrase.

Applicant submits that the above amendments and remarks overcome this rejection and its withdrawal is requested.

(J) The Examiner alleges that claim 35 is "indefinite as to the image of an internal region of a subject that is obtained and an omnibus claim."

In response, Applicant has amended claim 35 to define the internal image as of a tumor, and to further clarify the molecule of claim 2 as specific to target said tumor. Furthermore, by defining the internal image as of a tumor and by clarifying that the molecule (*i.e.*, peptide) of the invention as specific to target the image, Applicant has distinctly pointed out and claimed the invention.

Applicant submits that the above amendments and remarks overcome this rejection and its withdrawal is requested.

Applicant submits that the above amendments and remarks overcome or obviate these grounds for rejection under Section 112, second paragraph, and their withdrawal is requested.

THE REJECTION UNDER 35 U.S.C. § 101, SHOULD BE WITHDRAWN

The Examiner has rejected claim 12, 13, 31, and 34 under 35 U.S.C. § 101 as claiming the same invention as that of claims 1 and 2 of prior U.S. Patent No. 5,885,577. The Examiner has rejected claims 37 to 39, and 41 and 42 under 35 U.S.C. § 101 as claiming the same invention as that of claims 1 to 5 of prior U.S. Patent No. 6,015,561.

In response, Applicant respectfully points out that claims 13, 37 to 39, and 41 to 42 were canceled, without prejudice, in paragraph 2 of the Request for Filing a Continuation Application under 37 C.F.R. § 1.53(b) (a copy is attached hereto as Exhibit E). Applicant also respectfully points out that claims 12, 31, and 34 have been canceled, without prejudice. Thus, Applicant submits that the rejection has been obviated and respectfully requests withdrawal of the rejection.

THE REJECTION UNDER 35 U.S.C. § 102(a) OR § 102(e) OR ALTERNATIVELY UNDER 35 U.S.C. § 103, SHOULD BE WITHDRAWN

Claims 1 to 45 are rejected under 35 U.S.C. § 102(a) or 102(e) as anticipated

by or, in the alternative, under 35 U.S.C. § 103 as obvious over Kay [International PCT Publication No. WO 18318(a)(I) or U.S. Patent No. 5,498,538(II).

The Examiner alleges that:

> Kay (I), *e.g.*, par. bridging pp. 7-8 and page 73, lines 3-15; pp. 50-51; pp. 84-115, discloses a molecule obtained by a method of identifying a peptide which binds to a substance of interest comprising screening a first random peptide library with a ligand and identifying a peptide that specifically binds to said ligand and recites screening a second random peptide library with a compound comprising said first peptide to identify a peptide which binds to said compound. . . The claimed amino acid sequences are inherently or obviously possessed by the prior art peptide or molecule since the same antibody and screening methods as recited similarly employed by the prior art. The claimed antibodies peptides (abides, as coined by applicant) appear to be the same or similar to the prior art, absent a showing of unobvious differences. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the antibodies peptide sequences *i.e.*, that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is upon the applicants to prove that the claimed antibodies are functionally different from those taught by the prior art and to establish patentable differences. See in re Best 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (BPAI 1989).

Applicant respectfully disagrees with these rejections and with the Examiner's characterization of Kay.

The invention as presently claimed are molecules comprising peptides which mimic the binding specificity of an antibody (*e.g.*, claim 2). The invention as presently claimed also encompasses methods for identifying and methods for using peptides that mimic the binding specificity of an antibody (*e.g.*, claims 15, 23, 35, and 46).

THE LEGAL STANDARD

In analyzing the patentability of a claim to a product, courts have determined that patentability does not rely upon a difference in the method by which the product is made, but by whether the product is new and unobvious. In re Pilkington, 162 U.S.P.Q. 145, 147

(C.C.P.A. 1969). Therefore, "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself." In re Thorpe, 227 U.S.P.Q. 964, 966 (Fed. Cir. 1985). "When the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or 103 of the statute is eminently fair and acceptable." In re Brown, 459 F.2d 531, 535 (C.C.P.A. 1972) (emphasis added). Once the Examiner sets forth a *prima facie* case for anticipation and/or obviousness, the burden shifts to the Applicant "to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product." In re Thorpe, 227 U.S.P.Q. at 966.

In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 U.S.P.Q.2d 1081 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed. . . ." Structural Rubber Prod. Co. v. Park Rubber Co., U.S.P.Q. 1264 (Fed. Cir. 1984).

The objective standard for obviousness under 35 U.S.C. § 103 as set forth clearly by the Supreme Court of the United States in Graham v. John Deere Co., 383 U.S. 1 (1966) requires the Examiner to ascertain: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; and (3) the differences between the claimed subject matter and the prior art. *See* 383 U.S. at 17. The obviousness or nonobviousness of the claimed subject matter must be determined in light of these inquiries. Moreover, the Graham Court also explained that secondary considerations such as commercial success, long felt but unsolved needs, failure of others, *etc.* might be utilized in determining the obviousness or nonobviousness of the invention.

Following Graham, the Court of Customs and Patent Appeals (CCPA) and its present successor, the Court of Appeals for the Federal Circuit (CAFC), have held the following considerations to be objective evidence of nonobviousness: long felt need, commercial success, failure of others, copying and unexpected results. *See, e.g.,* Avia Group Int'l Inc. v. L.A. Gear California, Inc., 853 F.2d 1557, 7 U.S.P.Q.2d 1548 (Fed. Cir. 1988); In re Sernaker, 702 F.2d 989, 217 U.S.P.Q. 1 (Fed. Cir. 1983). In fact, the CAFC has consistently made clear that when evidence of such secondary considerations is present, it must be considered by the Examiner or a court in determining a question of obviousness. *See*

e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379-80, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); Stratoflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538-39, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983).

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter.

A finding of obviousness requires that the prior art suggest to those of ordinary skill in the art (1) that they should carry out the invention and (2) that they would have a reasonable expectation of success in so doing.

See In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991), where the Federal Circuit said:

> [A] proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.,* 837 F2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). [emphasis added]
>
> 947 F.2d at 493, 20 U.S.P.Q.2d at 1442.

Kay (PCT Publication WO 94/18318), at page 73, lines 3-15, discloses identifying immunogens for vaccines, useful for active immunization procedures, by

> generating a first series of TSARs specific for a given cellular or viral macromolecule ligand and then developing a second series of TSARs that bind to the first TSARs *i.e.,* the first TSAR is used as a ligand to identify the second series of TSARs. The second series of TSARs will mimic the initial cellular or viral macromolecule ligand site but will contain only relevant peptide binding sequences, eliminating irrelevant peptide sequences. Either the entire TSAR developed in the second series, or the binding domain, or a portion thereof, can be used as an immunogen for an active vaccination program.

As explained below, Kay does not describe the presently claimed methods for identifying a peptide which mimics the binding specificity of an antibody. Nor does Kay describe the molecules of the presently claimed invention that mimic the binding specificity of an antibody. In contrast, Kay describes a two-step process for identifying immunogens. Kay does not disclose nor suggest that molecules could be identified that mimic the binding

specificity of an antibody by using a two step process. Rather, Kay describes obtaining molecules (immunogens) that have the same immunogenicity as a given cellular or viral macromolecular ligand (see Kay, *i.e.*, WO 94/18318 at page 73, lines 4-15). Immunogens are antigens which elicit antibody production. The methods of the invention produce peptides that mimic antibody binding and thus bind an antigen of interest.

Prior to the present invention, there was no reasonable expectation that the binding of antibodies could be mimicked by much smaller molecules such as the abtides from the libraries described in the present application without the use of scaffolds to hold the abtides in proper configuration. When the prior art sought to mimic the binding of antibodies using peptide libraries, this was generally done by expressing naturally occurring antibody sequences, *e.g.*, entire variable region genes, cloned into phage or phagemid expression vectors. Implicit in the use of such large binding regions to mimic antibodies was the belief that relatively small peptides without defined structure, such as abtides, would not suffice to mimic the binding specificity of the much larger antibodies.

For example, in the prior art, McCafferty et al., 1990, Nature 348:552-554 (reference BT of the Information Disclosure Statement filed concurrently herewith) used PCR to amplify immunoglobulin variable (V) region genes and cloned those genes into phage expression vectors. The authors suggested that phage libraries of V, diversity (D), and joining (J) regions could be screened with antigen. The phage that bound to antigen could then be mutated in the antigen-binding loops of the antibody genes and rescreened. The process could be repeated several times, ultimately giving rise to phage which bind the antigen strongly.

Marks et al., 1991, J. Mol. Biol. 222:581-597 (reference BM of the Information Disclosure Statement filed concurrently herewith) also used PCR to amplify immunoglobulin variable (V) region genes and cloned those genes into phage expression vectors.

Kang et al., 1991, Proc. Natl. Acad. Sci. USA 88:4363-4366 (reference BP of the Information Disclosure Statement filed concurrently herewith) created a phagemid vector that could be used to express the V and constant (C) regions of the heavy and light chains of an antibody specific for an antigen. The heavy and light chain V-C regions were engineered to combine in the periplasm to produce an antibody-like molecule with a functional antigen binding site. Infection of cells harboring this phagemid with helper phage resulted in the

incorporation of the antibody-like molecule on the surface of phage that carried the phagemid DNA. This allowed for identification and enrichment of these phage by screening with the antigen. It was suggested that the enriched phage could be subject to mutation and further rounds of screening, leading to the isolation of antibody-like molecules that were capable of even stronger binding to the antigen.

Hoogenboom et al., 1991, Nucleic Acids Res. 19:4133-4137 (reference BO of the Information Disclosure Statement filed concurrently herewith) suggested that naive antibody genes might be cloned into phage display libraries. This would be followed by random mutation of the cloned antibody genes to generate high affinity variants.

In the prior art, peptide libraries have also been screened with receptors to identify receptor ligand-like peptides, but peptide libraries have not been considered useful for identifying such ligand-binding peptides as those that mimic receptors.

For example: Bass et al., 1990, Proteins: Struct. Func. Genet. 8:309-314 (reference BR of the Information Disclosure Statement filed concurrently herewith) fused human growth hormone (hGH) to the carboxy terminus of the gene III protein of phage fd. This fusion protein was built into a phagemid vector. When cells carrying the phagemid were infected with a helper phage, about 10% of the phage particles produced displayed the fusion protein on their surfaces. These phage particles were enriched by screening with hGH receptor-coated beads. It was suggested that this system could be used to develop mutants of hGH with altered receptor binding characteristics.

Lowman et al., 1991, Biochemistry 30:10832-10838 (reference BI of the Information Disclosure Statement filed concurrently herewith) used an improved version of the system of Bass et al. described above to select for mutant hGH proteins with exceptionally high affinity for the hGH receptor. The authors randomly mutagenized the hGH-pIII fusion proteins at sites near the vicinity of 12 amino acids of hGH that had previously been identified as being important in receptor binding.

Balass et al., 1993, Proc. Natl. Acad. Sci. USA 90:10638-10642 (reference AX of the Information Disclosure Statement filed concurrently herewith) used a phage display library to isolate linear peptides that mimicked a conformationally dependent epitope of the nicotinic acetylcholine receptor. This was done by screening the library with a monoclonal antibody specific for the conformationally dependent epitope. The monoclonal antibody used was thought to be specific to the acetylcholine receptor's binding site for its natural ligand,

acetylcholine.

With regards to amended claims 27 and 30 directed to compositions comprising the molecules of the presently claimed invention, Kay neither describes nor suggest such compositions for the same reason that the molecules are neither described nor suggested.

Furthermore, Applicant notes that claims 43 and 44 recite a certain structure. Claims 43 and 44 specify the structure of a peptide that binds to polymorphic epithelial mucin. Kay does not describe or suggest the structure of the peptide recited in claims 43 and 44, and thus these claims are not anticipated by or obvious over Kay.

Accordingly, Kay does not describe, suggest, nor provide a reasonable expectation of success of the presently claimed invention of molecules comprising peptides that mimic the binding specificity of a receptor or antibody and compositions thereof and methods for identifying and using the same. Therefore, the above remarks and amendments overcome or obviate the rejections under § 102 and/or §103, and their withdrawal is requested.

CONCLUSION

Applicant respectfully requests entry of the foregoing amendments and remarks into the file history of the above-identified application. Applicant believes that each ground for rejection or objection has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the application are respectfully requested.

Respectfully submitted,

Date April 24, 2001

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Enclosures

EXHIBIT A: MARKED UP VERSION OF THE SPECIFICATION

(U.S. APPLICATION NO. 09/484,879; ATTORNEY DOCKET NO. 1101-226)

On page 1, please amend the paragraph beginning "This application is", as follows:

This application is a continuation ~~-in-part~~ of ~~co-~~ ~~pending~~ U.S. Patent Application Serial No. **09/273,685, filed March 22, 1999, now U.S. Patent No. 6,015,561, which in turn is a division of U.S. Patent Application Serial No. 08/488,161 filed June 7, 1995, which issued as U.S. Patent No. 5,885,577 on March 23, 1999, which in turn is a continuation-in-part of co-pending U.S. Patent Application Serial No.** 08/310,192 filed September 21, 1994, **now abandoned,** the entire contents of which are incorporated herein by reference.

On page 9, please amend the paragraph beginning "The present invention", as follows:

The present invention relates to abtides. As used herein, the term "abtides" refers to peptides that mimic the binding specificity of a larger molecule such as an antibody or receptor. Abtides specifically bind to a ligand of interest, in which the ligand is a specific binding partner of the larger molecule (*e.g.* antibody or receptor). To identify the abtides of the present invention, peptide libraries are screened in a two-step process. The first screening step uses an antibody (or antigen-binding derivative thereof) or receptor (or ligand-binding derivative thereof) as a first target ligand. This step identifies peptide sequences termed "epitopes" or "mimetopes" which specifically bind the first target ligand. In the case where an antibody or derivative thereof is used as the first target ligand, a mimetope will often resemble, either functionally in terms of its binding capability and/or structurally in terms of its amino acid sequence, the epitope recognized by the antibody used as the first ligand. An epitope or mimetope is then used as a second target ligand in a second screening step to identify a peptide sequence that specifically binds the epitope or mimetope. Such peptides are known as "abtides." Surprisingly, it was found by the current ~~inventors~~ **inventor** and is demonstrated herein that abtides possess binding specificities strikingly similar to those possessed by the first target ligands (usually antibodies or receptors) described above.

On page 10, please amend the paragraph beginning "4. FIGURE LEGENDS", as follows:

4. ~~FIGURE LEGENDS~~ **BRIEF DESCRIPTION OF THE DRAWINGS**

On page 11, please amend the paragraph beginning "Figure 5 shows", as follows:

Figure 5 shows the binding of biotinylated mimetopes to immobilized abtides. □ represents binding of mimetope peptide Biotin-LYANPGMYSRLHSPA-NH_2 **(SEQ ID NO: 20)** to 7E11-C5 abtide clone 14; ○ represents binding of mimetope peptide Biotin-LYANPGMYSRLHSPA-NH_2 **(SEQ ID NO: 20)** to 7E11-C5 abtide clone 17; ◇ represents binding of mimetope peptide Biotin-GMYSRLH-NH_2 **(a portion of SEQ ID NO: 20)** to 7E11-C5 abtide clone 14; △ represents binding of mimetope peptide Biotin-GMYSRLH-NH_2 **(a portion of SEQ ID NO: 20)** to 7E11-C5 abtide clone 17. See Section 6.1.2.2 for details.

On page 12, please amend the paragraph beginning "Figure 10 schematically", as follows:

Figure 10 schematically illustrates the construction of the R26 TSAR library. The R26 expression library was constructed essentially as described for the TSAR-9 library that is described in PCT publication WO 94/18318, dated August 18, 1994, except for the modifications depicted in Figure 10. The oligonucleotide assembly process depicted in Figure 10 results in expression of peptides with the following amino acid sequence: $S(S/R)X_{12}\pi A\delta X_{12}SR$ (SEQ ID NO: ~~89)~~ **25)**, where π = S, P, T or A; and δ = V, A, D, E OR G **ctgtgcctcgagB(NNB)$_{12}$Nccgcgg is SEQ ID NO: 87; ctgtgctctaga(VNN)$_{12}$VNccgcgg is SEQ ID NO: 88, tcgagB(NNB)$_{12}$Nccgcgg is SEQ ID NO: 89; ctagt(VNN)$_{12}$VNccgcgg is SEQ ID NO: 90; SHSS(S/R)$X_{12}\pi A\delta X_{12}$SRPSRT is SEQ ID NO: 91**.

On page 12, please amend the paragraph beginning "Figure 11 schematically", as follows:

Figure 11 schematically illustrates the construction of the D38 TSAR library. The D38 expression library was constructed essentially as described for the TSAR-9 library that is described in PCT publication WO 94/18318, dated August 18, 1994, except for the

modifications depicted in Figure 11. **GTGTGTCTGCGAGN(NNB)$_{20}$NACGCCAN is SEQ ID NO: 92; GTTGTGTCTAGA(VNN)$_{15}$VNTGGCGTN is SEQ ID NO: 93; TCGAGN(NNB)$_{20}$NACGCCAN is SEQ ID NO: 94; CTAGA(VNN)$_{15}$VNTGGCGTN is SEQ ID NO: 95; HSS(S/R)X$_{20}$(Y/H/N/D)A(I/M/T/N/K/S/R)X$_{15}$SR is SEQ ID NO: 96.**

On page 12, please amend the paragraph beginning "Figure 12 schematically", as follows:

Figure 12 schematically illustrates the construction of the DC43 TSAR library. The DC43 expression library was constructed essentially as described for the TSAR-9 library that is described in PCT publication WO 94/18318, dated August 18, 1994, except for the modifications depicted in Figure 12. **GTGTGTCTCGAGN(NNB)$_{20}$GGTTGTGGT is SEQ ID NO: 97; GTTGTGTCTAGA(VNN)$_{20}$ACCACAACC is SEQ ID NO: 98; TCGAGN(NNB)$_{20}$GGTTGTGGT is SEQ ID NO: 99, CTAGA(VNN)$_{20}$ACCACAACC is SEQ ID NO: 100; HSS(S/R)X$_{20}$GCGX$_{20}$GCGX$_{20}$SR is SEQ ID NO: 101.**

On page 12, please amend the paragraph beginning "Figure 13 schematically", as follows:

Figure 13 schematically illustrates the oligonucleotides used to construct the polymorphic epithelial mucin (PEM) abtide saturation mutagenesis TSAR library (See Section 6.2.2).

GAPVWRGNPRWRGPGGFKWPGCGNGPMCNTGTPARGGSRNNGP is SEQ ID NO: 51; ggsgcsccsgtstgsagsggsaasccscgstgsagsggsccsggsggsttsaastgsccsGGCTGCGGG is SEQ ID NO: 102, sggsccsttsttscgsgasccsccscgsgcsggsgtsaasgtsttscasatsggsccsttCCCGCAGCC is SEQ ID NO: 103.

On page 20, please amend the paragraph beginning "Therefore, it is", as follows:

Therefore, it is contemplated that the most preferred binding domains for identifying the abtides of the present invention will be those from biologically expressed random peptide libraries in which the displayed peptide is 20 or greater amino acids in length. Examples of such random peptide libraries are the TSAR libraries, described ~~in~~ in PCT

publication WO 91/12328, dated August 22, 1991, and PCT publication WO 94/18318, dated August 18, 1994.

On page 27, please amend the paragraph beginning "As used in", as follows:

In an embodiment, a molecule comprises a peptide or a binding portion thereof which binds to a ligand of interest, which peptide is identified by a method comprising: screening a random peptide library with a ligand of interest, said ligand of interest being a peptide having a length of between 5 and 40 amino acids, to identify a peptide that specifically binds to the ligand of interest, in which the ligand of interest is also specifically bound by an antibody or a receptor.

In another embodiment, a molecule comprises a peptide which binds to a substance of interest, which peptide is identified by a method comprising: screening a random peptide library with a ligand, said ligand being a peptide of 36 amino acids or fewer, in which the ligand is an epitope of an antigen that is specifically bound by an antibody or in which the ligand represents the portion of a receptor-ligand that is responsible for the specific binding of the receptor to the receptor-ligand. As used in the present invention, a ligand is a substance for which it is desired to isolate a specific binding partner from a peptide library. A ligand can function as a lock, *i.e.*, a large polypeptide or protein analogous to a lock into which a smaller specific binding partner fits as a key; or a ligand can function as a key which fits into and specifically binds a larger binding partner or lock.

On page 28, please amend the paragraph beginning "A preferred method", as follows:

A preferred method for identifying abtides comprises screening a library of recombinant vectors that express a plurality of heterofunctional fusion proteins, said fusion proteins comprising (a) a binding domain encoded by an oligonucleotide comprising unpredictable nucleotides in which the unpredictable nucleotides are arranged in one or more contiguous sequences, wherein the total number of unpredictable nucleotides is greater than or equal to about 15 and less than or equal to about 600, and optionally, (b) an effector domain encoded by an oligonucleotide sequence which is a protein or peptide that enhances expression or detection of the binding domain. Screening is done by contacting the plurality

library with a compound comprising a first peptide identified by screening a first random peptide library with an antibody or antigen-binding derivative thereof that specifically binds to an antigen of interest, thereby identifying a second peptide which binds to said compound and which mimics the binding specificity of said antibody.

EXHIBIT C: MARKED UP VERSION OF THE CLAIMS

(U.S. APPLICATION NO. 09/484,879; ATTORNEY DOCKET NO. 1101-226)

2. (amended) A molecule comprising a peptide which [binds to an antigen of interest] mimics the binding specificity of an antibody, which peptide is identified by a method comprising:

(a) screening a first random peptide library with an antibody or antigen-binding derivative thereof that specifically binds to an antigen of interest, to identify a first peptide that specifically binds to said antibody or antigen-binding derivative thereof; and

(b) screening a second random peptide library which is the same or different from said first random peptide library with a compound comprising said first peptide identified in step (a) or a specific binding portion thereof, to identify a second peptide which binds to said compound and which [binds to said antigen of interest] mimics the binding specificity of said antibody.

6. (amended) [The] A molecule comprising a peptide which mimics the binding specificity of an antibody, which peptide is identified by a method comprising:

(a) screening a first random peptide library with an antibody or antigen-binding derivative thereof, to identify a plurality of different first peptides each of which specifically binds to said antibody or antigen-binding derivative thereof;

[of claim 2, in which said method further comprises]

(b) comparing the sequences of [a] said plurality of different first peptides identified as binding said antibody or antigen-binding derivative thereof in step (a), to identify a consensus binding sequence; and

(c) screening a second random peptide library which is the same or different from said first random peptide library with a compound comprising said consensus binding sequence, to

identify a second peptide which binds to said compound and which mimics the binding specificity of said antibody[, in which said compound of step (b) comprises said consensus binding sequence].

8. (amended) The molecule of claim 2 in which the antibody is the monoclonal antibody 7E11-C5 which is a murine IgG1 monoclonal antibody which binds specifically to human prostate carcinoma cell line LNCaP, as produced by the hybridoma deposited with the ATCC and assigned accession number HB 10494.

10. (amended) The molecule of claim 2 in which the library of step (a) or step (b) is a library of recombinant vectors that express a plurality of heterofunctional fusion proteins comprising random peptides, said fusion proteins comprising a binding domain encoded by an oligonucleotide comprising unpredictable nucleotides in which the unpredictable nucleotides are arranged in one or more contiguous sequences, wherein the total number of unpredictable nucleotides is greater than or equal to about 15 and less than or equal to about 600, and an effector domain that enhances expression or detection of the binding domain.

15. (amended) A method of identifying a peptide which [binds to an antigen of interest] mimics the binding specificity of an antibody, which [peptide is identified by a] method [comprising] comprises:

(a) screening a first random peptide library with an antibody or antigen-binding derivative thereof that specifically binds to an antigen of interest, [to identify] and thereby identifying a first peptide that specifically binds to said antibody or antigen-binding derivative thereof; and

(b) screening a second random peptide library which is the same or different from said first random peptide library with a compound comprising said first peptide identified in step (a) or a specific binding portion thereof, [to identify] and thereby identifying a second peptide which binds to said compound and

which [binds to said antigen of interest] mimics the binding specificity of said antibody.

16. (amended) The method of claim [14] 15, in which said first random peptide library is a different library from said second random peptide library.

17. (amended) The method of claim [14] 15, in which said first random peptide library is the same library as said second random peptide library.

19. (amended) The method of claim 15 in which the antibody is the monoclonal antibody 7E11-C5 which is a murine IgG1 monoclonal antibody which binds specifically to human prostate carcinoma cell line LNCaP, as produced by the hybridoma deposited with the ATCC and assigned accession number HB 10494.

21. (amended) The method of claim 15 in which the library of step (a) or step (b) is a library of recombinant vectors that express a plurality of heterofunctional fusion proteins, said fusion proteins each comprising (a) a random peptide comprising a binding domain encoded by an oligonucleotide comprising unpredictable nucleotides in which the unpredictable nucleotides are arranged in one or more contiguous sequences, wherein the total number of unpredictable nucleotides is greater than or equal to about 15 and less than or equal to about 600, and (b) an effector domain that enhances expression or detection of the binding domain.

23. (amended) A method of detecting or measuring an analyte of interest in a sample, comprising:

(a) contacting a sample with a molecule comprising a peptide capable of specifically binding said analyte of interest under conditions such that specific binding between said molecule and said analyte can occur; and

(b) detecting or measuring the amount of said binding in which the presence and amount of said binding indicates the presence and amount, respectively, of said analyte in the sample;

in which said peptide is identified by the method of claim [14] 15.

27. (amended) A [therapeutic or diagnostic] composition comprising the molecule of claim 2; and a [pharmaceutically acceptable] carrier.

30. (amended) A [therapeutic or diagnostic] composition comprising the molecule of claim 8; and a pharmaceutically acceptable carrier.

33. (amended) A molecule comprising a peptide or a binding portion thereof which [binds to a ligand of interest] mimics the binding specificity of a receptor molecule, which peptide is identified by a method comprising: screening a random peptide library with a ligand of interest, said ligand of interest being a peptide having a length of between 5 and 40 amino acids, to identify a peptide that specifically binds to the ligand of interest, in which the ligand of interest is also specifically bound by an antibody [or a receptor].

35. (amended) A method of obtaining an image of an internal region of a subject, wherein said internal image is of a tumor, comprising administering to said subject an effective amount of the molecule of claim [1] 2, wherein said molecule specifically targets said tumor, in which said molecule is radiolabeled with a radioactive metal, and recording the scintigraphic image obtained from the decay of said radioactive metal.

36. (amended) A molecule comprising a peptide which [binds to a substance of interest] mimics the binding specificity of an antibody, which peptide is identified by a method comprising: screening a random peptide library with a ligand, said ligand being a peptide of 36 amino acids or fewer, in which the ligand is an epitope of an antigen that is specifically bound by [an] said antibody or in which the ligand represents the portion of a receptor-ligand that is responsible for the specific binding of the receptor to the receptor-ligand.

46. (new) A method for identifying a peptide which mimics the binding specificity of an antibody, which method comprises: screening a second random peptide

of heterofunctional fusion proteins with a ligand under conditions conducive to ligand binding and then isolating the fusion proteins which bind to the ligand. The methods of the invention further preferably comprise determining the nucleotide sequence encoding the binding domain of the heterofunctional fusion protein identified to determine the DNA sequence that encodes the binding domain and simultaneously to deduce the amino acid sequence of the mimetope used in the second screen. Nucleotide sequence analysis can be carried out by any method known in the art, including but not limited to the method of Maxam and Gilbert (1980, Meth. Enzymol. 65:499-560), the Sanger dideoxy method (Sanger et al., 1977, Proc. Natl, Acad. Sci. U.S.A. 74:5463), the use of **SEQUENASE™** T7 DNA polymerase (Tabor and Richardson, U.S. Patent No. 4,795,699; ~~Sequenase™~~; U.S. Biochemical Corp.), or ~~Taq~~ **TAQ™** polymerase, or use of an automated DNA sequenator (*e.g.*, Applied Biosystems, Foster City, CA).

On page 41, please amend the paragraph beginning "(a) Polystyrene microtiter wells", as follows:

(a) Polystyrene microtiter wells (Flow Laboratory) are coated overnight at room temperature with 100 µl of a solution of a molecule comprising an abtide at a concentration of 1 mg/ml in phosphate buffered saline (PBS).

(b) Coating solution is discarded and wells are blocked for 1-2 hours at room temperature with 300 µl of 1% bovine serum albumin (BSA) in phosphate-buffered saline (PBS) with 0.05% of ~~Tween 20~~ ~~(PBS-Tween~~**"TWEEN™" 20 (polyoxyethylenesorbitan monolaurate) (PBS-TWEEN™** buffer).

(c) 150 µl of sample (suspected of containing an analyte the presence or amount of which it is desired to measure) diluted in 1% BSA-PBS is added per well. Wells are incubated 1 hour at room temperature.

(d) Wells are washed 4 times with PBS-~~Tween~~ **TWEEN™** buffer.

(e) 100 µl of horseradish peroxidase conjugated monoclonal antibody specific for the analyte in 1% BSA-PBS is added per well. The concentration of the monoclonal antibody can be from about 10 ng/ml to 10 mg/ml. Wells are incubated 1 hour at room temperature.

(f) Wells are washed 6 times with PBS -~~Tween~~ **TWEEN™** buffer.

(g) 100 µl of ABTS® Boehringer Mannheim (2,2′-Azino-di-[3-ethylbenzthiazdine sulfonate (6)] crystallized diammonium salt working solution is added per well. ABTS® stock solution is prepared at 15 mg/ml in dH_2O. To make the working solution, 200 µl of this ABTS® stock is diluted into 10 ml of citrate phosphate buffer (17 mm citric acid, 65 mm dibasic sodium phosphate) and 10 µl 30% H_2O_2.

(h) The absorbance of each well is measured at 405 nm in a microtiter plate reader (Dynatech MR600, Dynatech Corp., Alexandria, VA.).

On page 45, please amend the paragraph beginning "Abtides may be", as follows:

Abtides may be linked to chelators such as those described in U.S. Patent No. 4,741,900 or U.S. Patent No. 5,326,856. The abtide-chelator complex may then be radiolabeled to provide an imaging agent for diagnosis or treatment of disease. The abtide may also be used in the methods that are disclosed in co-pending U.S. patent application serial no. 08/127,351**, now U.S. Patent No. 5,449,761,** for creating a radiolabeled peptide for use in imaging or radiotherapy. This application contains a review of methods of using peptides in imaging agents.

On page 49, please amend the paragraph beginning " By way of", as follows:

By way of example but not limitation, peptides can be synthesized on an Applied Biosystems Inc. ("ABI") model 431A automated peptide synthesizer using the "Fastmoc" synthesis protocol supplied by ABI, which uses 2-(1H-Benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate ("HBTU") (R. Knorr et al., 1989, Tet. Lett., 30:1927) as coupling agent. Syntheses can be carried out on 0.25 mmol of commercially available 4-(2',4'-dimethoxyphenyl-(9-fluorenyl-methoxycarbonyl)-aminomethyl)-phenoxy polystyrene resin ("Rink resin" from Advanced ChemTech) (H. Rink, 1987, Tet. Lett. 28:3787). Fmoc amino acids (1 mmol) are coupled according to the ~~Fastmoc~~ **FASTMOC™** protocol. The following side chain protected Fmoc amino acid derivatives are used: FmocArg(Pmc)OH;

FmocAsn(Mbh)OH; FmocAsp(^{t}Bu)OH; FmocCys(Acm)OH; FmocGlu(^{t}Bu)OH; FmocGln(Mbh)OH; FmocHis(Tr)OH; FmocLys(Boc)OH; FmocSer(^{t}Bu)OH; FmocThr(^{t}Bu)OH; FmocTyr(^{t}Bu)OH. [Abbreviations: Acm, acetamidomethyl; Boc, tert-butoxycarbonyl; ^{t}Bu, tert-butyl; Fmoc, 9-fluorenylmethoxycarbonyl; Mbh, 4,4'-dimethoxybenzhydryl; Pmc, 2,2,5,7,8-pentamethylchroman-6-sulfonyl; Tr, trityl].

On page 53, please amend the paragraph beginning "In order to", as follows:

In order to identify abtides mimicking binding specificity of monoclonal antibody 7E11-C5, monoclonal antibody 7E11-C5 was used as the target ligand in a first screening of the TSAR-9 library (see Kay et al., 1993, Gene 128:59-65 and PCT publication WO 94/18318, dated August 18, 1994). The following screening procedure was used. First, 7E11-C5 was bound to a well of a microtiter plate. 7E11-C5 at a concentration of 11.2 mg/mL in phosphate buffered saline (PBS), pH 6.0, was diluted to 100 μg per mL in 0.1x PBS pH 7.2. One hundred microliters (100 μL) of this dilution was added to one well of a microtiter plate, and allowed to incubate for 1-6 hours at room temperature or overnight at 4° C. After incubation, the well was washed at least 4 times with a blocking buffer which consisted of either 1% bovine serum albumin (BSA) in PBS, 1% non-fat dry milk (NFDM) in PBS, or 0.1% ~~Tween®~~TWEEN™ in either 1% BSA in PBS or 1% NFDM in PBS. Two hundred microliters of the blocking buffer was then added to the well and allowed to incubate for at least an hour at room temperature.

On page 54, please amend the paragraph beginning "Next, an aliquot", as follows:

Next, an aliquot of the TSAR-9 library was added to the well containing bound 7E11-C5. An aliquot of the library containing 10^{10} phage particles was added to the well and allowed to incubate for at least 1 hour at room temperature. This resulted in the binding to the plate of those phage containing binding domains that bind to 7E11-C5. After an hour, the well was washed extensively with either 1% bovine serum albumin (BSA) in PBS, 1% non-fat dry milk (NFDM) in PBS, or 0.1% ~~Tween®~~TWEEN™ in either 1% BSA in PBS or 1% NFDM in PBS.

On page 56, please amend the paragraph beginning "Using the above", as

follows:

Using the above procedures, nine different phage were isolated that expressed peptides containing binding domains that were capable of binding monoclonal antibody 7E11-C5. Molecules comprising these binding domains are thus mimetopes of the antigen recognized by the monoclonal antibody 7E11-C5. The binding domains of the peptides expressed by the nine phage were sequenced according to standard methods of DNA sequencing ~~(Sequenase ™~~**(SEQUENASE™**, U.S. Biochemical Corp., Cleveland, OH). The determination of those DNA sequences allowed the determination of the amino acid sequences of these mimetopes. These sequences are shown in Table 1. Examination of these amino acid sequences showed that they shared a common motif of MYxxLH (SEQ ID NO. 10).

On page 60, please amend the paragraph beginning "In some cases,", as follows:

In some cases, these abtides were used in a dot blot experiment. In those cases, 1 μL of a 1 mg/mL solution of the 38-residue abtides was spotted onto nitrocellulose (0.2 μm or 0.45 μm, Schleicher & Schuell, Keene, NH) strips or circles. After drying (about ~~1/2~~½ hour), the nitrocellulose was blocked for 1 hour in a solution of 1% BSA in PBS. The nitrocellulose was then allowed to incubate in approximately 5 mL of a solution of 0.1 mg/mL of a biotinylated 7E11-9.5 mimetope peptide (biotin-LYANPGMYSRLHSPA~~)~~-**NH_2 (SEQ ID NO: 20)**. This mimetope peptide was one of those described in Section 6.1.1 above that were synthesized based upon the nine peptides that were identified in the screening of Section 6.1.1 above. After an hour, the nitrocellulose was washed approximately 5 times with a solution of 1% BSA in PBS. A 1:2000 dilution of Extravidin-Alkaline Phosphatase (4,250 units/mL) (Sigma, St. Louis, MO) in PBS was then added and allowed to incubate for 1 hour, after which the nitrocellulose was again washed extensively. Finally, a solution of 5-bromo-4-chloro-3-indolyl phosphate (0.15 mg/mL) and nitro blue tetrazolium (0.3 mg/mL) (Sigma, St Louis, MO) (BCIP/NBT) was added as an enzyme substrate. Color was allowed to develop and the absorbance at 405 nm was read.

On page 65, please amend the paragraph beginning "For biodistribution studies,", as follows:

For biodistribution studies, abtides were modified at their amino termini with the chelator diethylene-triamine-pentaacetic acid anhydride (DTPA-A) (Sigma, St. Louis, MO). Approximately 2 mg of each abtide was initially dissolved in an appropriate volume of 0.1% acetic acid and then 1 mL of 0.1 M sodium bicarbonate, pH 8.0, was added. Two mg of DTPA-A was suspended in 100 µL of dimethylsulfoxide (DMSO), and 10 µL of the abtide solution added to this DTPA-A suspension. After 5 min incubation at room temperature, the suspension was filtered through a 0.2 µm **ACRODISC™** polyvinylidene difluoride (PVDF) sample filter ~~(Acrodisc~~**(ACRODISC™**, Gelman Sciences, Inc., Ann Arbor, MI), and purified using a Superose-12 FPLC column (Pharmacia, Piscataway, NJ) with PBS as the running buffer. Modified peptides were stored frozen at -20° C or -70° C.

On page 76, please amend the paragraph beginning "Negative Binding Sequences", as follows:

Negative Binding Sequences

MPI **G**APVWRGNPRWRGPGGFKWPGCGNGPMCNTFTPARGGSRNNGP (SEQ ID NO: 51)

E3 **G**TRVPPGFALRGGRDGLSWAGCGKA**P**ISKTYTSARGRSRKK**G**S (SEQ ID NO: 77)

E15 RSAVSEG**K**PREIVPGGCMWPGCGNGRKSNTLTHGPEQFQEIEP (SEQ ID NO: 78)

E24 SSGVGNG**K**PRS**W**APDALNGGCGNIQFANTITPDRGGSCNQTL (SEQ ID NO: 79)

E27 **G**SSVCGGQPSGRGFGGLPGPGCGNG**P**TSNTLTSARGGFPNK**G**L (SEQ ID NO: 80)

E37 **GA**PL**W**QGDPADEVLGGSMIPGCGIGALSQTFT**P**TPGGSRKNVT (SEQ ID NO: 81)

E43 AGRELRQDEGEGGAGADVARLREGPICSTFTPARGGSCPSGL (SEQ ID NO: 82)

E49 QA**R**VSMAISCRSGPSDLMHQGCGYG**P**RCNPDTTDSGGSHTNTP (SEQ ID NO: 83)

E60 **G**DPECRG**K**PRGRWTGSLACTGCGNG**P**NSKICTRARGVSRNK**G**P (SEQ ID

NO: 84)

E72 STPGCSGYSGSGDPRCLTCTACGNGHTRKTLTPAHGRSTHKEP (SEQ ID NO: 85)

E34 GQPECRITSGCCGTDGNKWLGCGKVDMCNTLNPAVGCHGTNGS (SEQ ID NO: 86)

E83 REPVVGGKPWCRGPGGLRWRGCGKSQFDKIITLSRDNRRDKRP (SEQ ID NO: ~~87)~~ 23)

On page 77, please amend the paragraph beginning "When the sequences", as follows:

When the sequences shown in Table 7 are compared (see particularly the amino acid residues marked in boldface type), it is possible to determine the influence of particular amino acid residues at specific positions in the sequence on a peptide's ability to bind to PEM. Abtides that bind to PEM can be characterized by the formula:

~~R1R2R3R4R5R6R7R8R9R9R10R11R12R13R14R15R16R17R18R19R20R21R22R23R24R25R26R27R28R29~~

$R_1R_2R_3R_4R_5R_6R_7R_8R_9R_{10}R_{11}R_{12}R_{13}R_{14}R_{15}R_{16}R_{17}R_{18}R_{19}R_{20}R_{21}R_{22}R_{23}R_{24}R_{25}R_{26}R_{27}R_{28}R_{29}$
$R_{30}R_{31}R_{32}R_{33}R_{34}R_{35}R_{36}R_{37}R_{38}R_{39}R_{40}R_{41}R_{42}R_{43}$ (SEQ ID NO: ~~88)~~ 24)

where:

R_1= G, C, E, or V, preferably G;

R_2= A, S, P, or L, preferably A;

R_3= P, T, H, or L, preferably P;

R_4= L, M, Q, G, A, or S;

R_5= W or Y, preferably W;

R_6= S, C, K or T, preferably S;

R_7= E, S, C, D, V, or R;

R_8= N, H, K, S, or E;

R_9= L, H, R, N, Q, T, or G;

R_{10}= W, P, R, T, or D, preferably W;

R_{11}= W, C, V, L, or G, preferably W;

R_{12}= S, T, M, or H, preferably S or T;

R_{13}= G;

R_{14}= S, A, G, N, Q, or H, preferably S;

R_{15}= W, H, G, A, or R;

R_{16}= G, T, E, P, V, or W, preferably G;

R_{17}= V, F, W, K, or A;

R_{18}= K, Q, D, E, R, or L, preferably K;

R_{19}= R, F, or S, preferably R;

R_{20}= P, S, I or H, preferably P;

R_{21}= G;

R_{22}= C;

R_{23}= G;

R_{24}= D, S, T, N, or H;

R_{25}= G, D, L, or R;

R_{26}= P or S, preferably P;

R_{27}= M, S, D, I, L, or R;

R_{28}= G, W, C, L, F, Y, or T, preferably G or W;

R_{29}= S, N, V, F, H, or R;

R_{30}= N, A, S, M, or R, preferably N;

R_{31}= F, Q, P, or V, preferably F;

R_{32}= S, V, I, K, A, or S;

R_{33}= P, A, N, or Y, preferably P;

R_{34}= G, N, or L;

R_{35}= K, R, C, Q or L, preferably K or R;

R_{36}= V, K, R, or A;

R_{37}= G, D, A, or E, preferably G;

R_{38}= S, T, P, Y or W; preferably S;

R_{39}= R, I, L, P, A or S;

R_{40}= N, K, or M, preferably N or K;

R_{41}= S, R, T, E, Q, P, Y or H;

R_{42}= G, A, S, D, N, P, Y, or K, preferably G;

R_{43}= P, H or A.